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Two Rare Exon 21 *EGFR* Mutations in Patients Treated with Gefitinib

To the Editor:

Treatment of non–small-cell lung cancer patients with reversible inhibitors of the tyrosine kinase domain of epidermal growth factor receptor (EGFR), gefitinib and erlotinib, in patients with *EGFR* mutations result in 70% to 80% responses.[1,2] Ninety percent of these consist of deletions of exon 19 and p.L858R mutations on exon 21.[2] However, through diverse mechanisms[3] resistance will eventually appear. There are also a minority of infrequent *EGFR* mutations at diagnosis whose predictive role is poorly characterized.[4]

We present two cases of patients diagnosed with a lung adenocarcinoma harboring rare *EGFR* mutations that received treatment with gefitinib. Mutational analysis was performed by polymerase chain reaction amplification of exons 18, 19, 20 and 21 of the *EGFR* gene and exon 1 of the *KRAS* gene followed by direct sequencing using BigDye 3.1 (Applied Biosystems, Foster City, CA) and analysis in a Genetic Analyzer 3500Dx (Applied Biosystems).

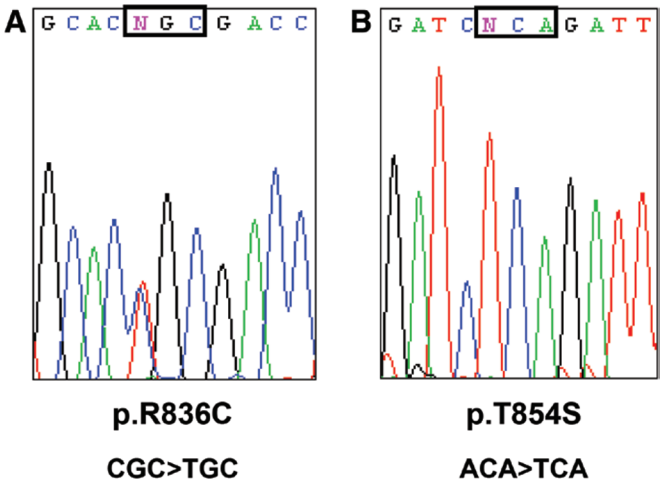

FIGURE 1. Sequencing chromatograms showing EGFR mutations affecting cases 1 and 2. *A*, Case 1-arginine(R) to cysteine (C) substitution at amino acid position 836 (p.R836C) resulting from a CGC→TGC exchange. *B*, Case 2-threonine (T) to serine (S) substitution at amino acid position 854 (p.T854S) resulting from a ACA→TCA exchange.

CASE 1

A white, 81-year-old, male exsmoker was diagnosed in July 2010 of a stage IIIA (T4N0M0) lung adenocarcinoma. Molecular analysis demonstrated the presence of a p.R836C mutation in exon 21 of the *EGFR* gene. He began first-line chemotherapy with a platinum doublet. Response assessment by computed tomography scan showed stabilization. However, because of symptomatic progression he started treatment with gefitinib 250 mg/day. In January 2011 he was admitted in hospital because of increasing dyspnoea and pain. The computed tomography scan showed progression of the tumor with appearance of pleural effusion. The study of the fluid confirmed the diagnosis of metastasis from adenocarcinoma harboring the p.R836C mutation on exon 21 (Fig. 1A). No p.T790M mutation on exon 20 or hepatocyte growth factor receptor (MET) amplification was detected. Progressive disease led to rapid deterioration of performance status and the patient died in early March 2011.

CASE 2

A white, 54-year-old, heavy smoker man was diagnosed in May 2011 with a lung adenocarcinoma stage IIIB (T4N2M0) not suitable for radical treatment. Evaluation of *EGFR* mutational status demonstrated the presence of the p.T854S mutation in exon 21. No wild-type allele was detected in this position, indicating that the mutation was either hemizygous or homozygous (Fig. 1B). He started treatment with gefitinib and early (6 weeks) assessment by computerized tomography demonstrated progressive disease. He received subsequent lines of treatment with stable disease as best response. Local and central nervous system progression led

Disclosure: The authors declare no conflict of interest.

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to important clinical deterioration and death in March 2012.

DISCUSSION

The finding of *EGFR* mutations not previously described always confers the challenge of treatment decision. For this reason we report these cases of patients with infrequent *EGFR* mutations on exon 21 with rapid progression on gefitinib treatment. Upcoming results of newly available EGFR inhibitors such as afatinib or dacomitinib will show whether these drugs will be effective for this subset of patients.

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